Comparison of 2 Treatment Strategies for Depressed Inpatients: Imipramine and Lithium Addition or Mirtazapine and Lithium Addition

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Background: The purpose of this study was to compare the overall effectiveness of 2 treatment strategies for inpatients with severe major depressive episode (DSM-III-R): (1) mirtazapine (phase 1) and subsequent lithium addition (phase 2) or (2) imipramine (phase 1) and subsequent lithium addition (phase 2). We previously reported the results of phase 1.

Method: In phase 1, patients were randomly assigned to treatment with either mirtazapine or imipramine, and doses were adjusted to obtain predefined blood drug levels. Nonresponders had lithium added to the double-blind mirtazapine or imipramine medication. The dose was adjusted to obtain a blood lithium level of 0.5–1.0 mmol/L. Treatment effects were evaluated weekly by the Montgomery-Asberg Depression Rating Scale for up to 2 weeks on this blood lithium level.

Results: Data for 100 patients were available for comparison of the 2 treatment strategies. 80 patients received no comedication. By the end of phase 2, 24 (48%) of 50 had responded to mirtazapine and 32 (64%) of 50 had responded to imipramine (intent-to-treat analysis). A survival analysis of the total patient group intent-to-treat showed a significant difference in favor of the treatment strategy with imipramine and subsequent lithium addition.

Conclusion: Efficacy of imipramine and subsequent lithium addition for nonresponders is superior to the same treatment strategy with mirtazapine. This applies to the patient sample studied, which consisted of 100 severely depressed inpatients, 29 of whom were psychotically depressed. More serious side effects of imipramine, however, led to discontinuation of imipramine in 5 patients. No serious side effects were observed during the phase of lithium addition to either imipramine or mirtazapine. We, therefore, prefer to start treatment with imipramine and test for fixed blood drug levels, and, if necessary, add lithium. In the case of prohibitive side effects, patients are switched to a modern antidepressant such as mirtazapine, and, if necessary, lithium is added to this antidepressant.

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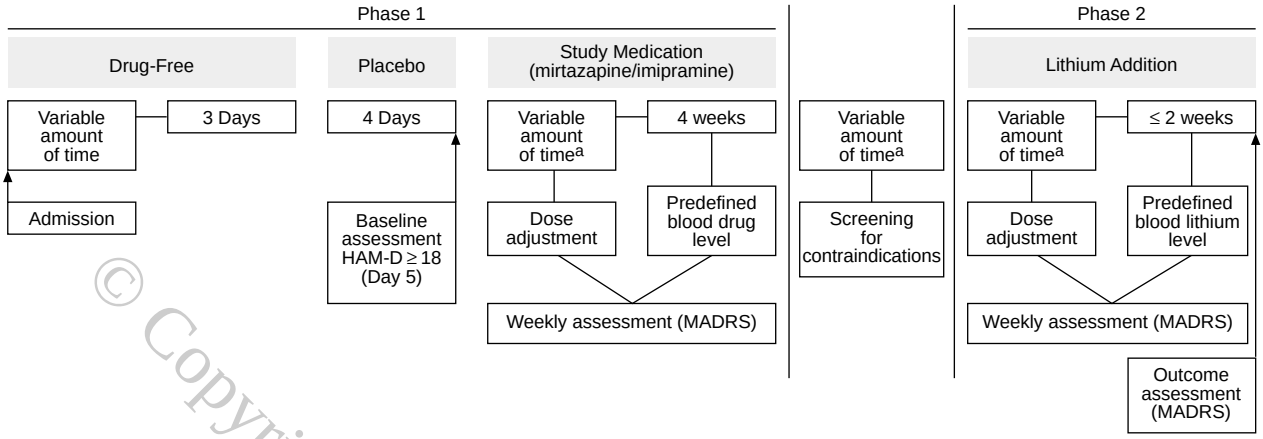
Many clinical reports and open studies and a few double-blind studies suggest lithium addition to be an effective strategy for treatment-resistant depression in about 50% to 60% of cases.[1] Although most double-blind studies deal with small numbers of patients,[2–8] 2 meta-analyses of these studies confirm the effectiveness of lithium addition.[8,9]

As a result, it is quite common in clinical practice to add lithium to an antidepressant in the case of nonresponse to the latter. The treatment with an antidepressant and the addition of lithium to it, however, are seen as separate, unrelated treatment decisions; e.g., in prescribing an antidepressant, clinicians do not take into account the efficacy of a possible lithium addition with that particular antidepressant, although results of lithium addition may differ between antidepressants. Similarly, in studies of lithium addition, nonresponders to an antidepressant are mostly recruited without much attention for details of the treatment phase that resulted in nonresponse.[1,8]

In the present study, lithium was added to the treatment of inpatients who were treatment-resistant in a randomized, double-blind, fixed blood level study comparing mirtazapine with imipramine. Mirtazapine is a new antidepressant of the group of the piperazinoazepines, related to mianserin. It is a strong antagonist of central α_2-adrenoceptors, serotonin 5-HT_2 and 5-HT_3 receptors, and histamine H_1 receptors and is a weaker antagonist of muscarine and α_1-adrenoceptors.[10] The results of the comparative trial, before lithium addition, indicated a large, statistically significant and clinically relevant difference in efficacy in favor of imipramine.[11]

The purpose of the present study was to compare the overall response of a 2-step treatment strategy with a stan-

Figure 1. General Outline of the Study Design



[a]See the section titled "Results: Patient Population and Dropouts."

dard tricyclic antidepressant and lithium addition for nonresponders with a similar treatment strategy with mirtazapine and subsequent lithium addition.

METHOD

Phase 1: Double-Blind Study Medication Period

For a detailed description of the double-blind part of the study, the reader is referred to our previous report.[11] The general outline is presented in Figure 1. The study was performed at the inpatient depression unit of the Department of Psychiatry of the University Hospital Dijkzigt Rotterdam, where uncomplicated depressed patients as well as treatment-resistant depressed patients are treated. Included were patients aged 18–65 years who had a DSM-III-R diagnosis of major depressive episode,[12] which was assessed by 2 psychiatrists performing the depression part of the Schedule for Affective Disorders and Schizophrenia (SADS)[13] and a Hamilton Rating Scale for Depression (HAM-D)[14] score ≥ 18. Patients with hallucinations, schizophrenia, paranoid psychosis, organic brain syndrome, chronic drug or alcohol abuse, or clinically relevant somatic disease were excluded.

After giving written informed consent, patients were randomly allocated to double-blind treatment. Treatment was started with either 75 mg/day of imipramine or 20 mg/day of mirtazapine. After 2 days, the dose was doubled unless severe side effects were observed. Blood drug levels were monitored weekly, and doses of both drugs were adjusted (by an independent psychiatrist to preserve blindedness) to obtain fixed blood drug levels (200–300 µg/L for imipramine + desmethylimipramine and 50–100 µg/L for mirtazapine). Response was assessed weekly with the Montgomery-Asberg Depression Rating Scale (MADRS).[15] No psychotropic medication besides the study medication was allowed except for 1 to 6 tablets per day containing 45 mg of an extract of valerian in case of anxiety or insomnia. This extract was assumed to be without antidepressant effect. In exceptional cases, lorazepam, 1 to 5 mg/day, for intolerable agitation or anxiety, or haloperidol, 1 to 15 mg/day, in case of intolerable psychotic symptoms, was prescribed.

Phase 2: Lithium Addition Period

Four weeks after attainment of the predefined blood level of mirtazapine or imipramine, nonresponders had lithium added to the double-blind medication. After screening for contraindications (thyroid, cardiac, or renal disease), lithium was started at a daily dose of 200 to 800 mg at 8 p.m. After 5 to 7 days, the blood lithium level was monitored at 8 a.m., and weekly thereafter at 8 a.m. The dose was adjusted to obtain as soon as possible a blood level of 0.5 to 1.0 mmol/L. The effect of lithium addition was evaluated weekly by assessment with the MADRS, up to 2 weeks after reaching the blood level of 0.5 to 1.0 mmol/L. Administration of the mirtazapine/imipramine medication was kept blind throughout the trial period.

Data Analysis and Statistical Methods

The results of the sequential treatment strategies were evaluated with survival analysis using the Cox proportional hazards model. Duration of treatment until meeting the response criterion was the survival time variable. Response was defined as a 50% or more reduction in the baseline MADRS score. During phase 1, the last time this response was assessed was at 4 weeks after attainment of the predefined blood drug level, unless the response criterion was met earlier. During lithium addition, the last time response was assessed was at 2 weeks after attainment of the blood lithium level of 0.5 to 1.0 mmol/L, unless the response criterion was met earlier. Dropouts were censored at the time of dropout. Eventual nonresponders were censored at the end of the treatment strategy, i.e., 2 weeks after attaining the blood lithium level of 0.5 to 1.0

mmol/L. As planned a priori,[11] the analyses for testing differences in response rates between the 2 treatment strategies were adjusted for the following covariables and their possible interactions with type of treatment: MADRS pretreatment scores (baseline severity), duration of the current episode, adequate pretreatment during current episode, number of previous depressive episodes, bipolar type, melancholic type, psychotic features, type of depression according to Research Diagnostic Criteria, and time to attain predefined blood level of study medication. A survival analysis with start time of haloperidol as time-dependent covariable was performed to take into account the possible influence of haloperidol comedication on response. Each covariable and, consecutively, this covariable with its interaction with type of treatment were entered in a model containing type of treatment only. A p value < .05 (2-sided) was considered statistically significant. Eventually, a model was fitted containing all covariables and interactions that had thus appeared to be significant. Hazard ratios with 95% confidence intervals (CIs) are presented. The hazard ratio is the factor by which the response rate is multiplied for each unit increase in the covariable. Thus, if the covariable is dichotomous (e.g., treatment type), then the hazard ratio is the ratio of the response rate in one group (e.g., mirtazapine with lithium addition) relative to the other (e.g., imipramine with lithium addition).

Adequate pretreatment during current episode was defined as an adequate dose of an antidepressant received for at least 4 weeks.[16]

The efficacy of lithium addition as such (the effect in phase 2) in nonresponders was not analyzed separately because the difference in efficacy between imipramine and mirtazapine in phase 1 makes nonresponders taking imipramine and nonresponders taking mirtazapine no longer representative of the same pool of patients.

RESULTS

Patient Population and Dropouts

One hundred seven depressed inpatients were randomly assigned to either mirtazapine (N = 54) or imipramine (N = 53). Seven patients (4 taking mirtazapine and 3 taking imipramine) did not receive lithium addition although they were nonresponders; 1 patient recovered shortly after addition of haloperidol, 1 patient was discharged without our consent, and 5 patients were continued on double-blind medication without ever receiving lithium addition. Thus, 100 patients were available for analysis (Table 1). During phase 1, 8 patients dropped out, while 2 patients were excluded from analyses because monitoring of blood levels showed noncompliance (Table 2). Thus, 90 patients (47 taking mirtazapine and 43 taking imipramine) remained after phase 1. The mean ± SD time to reach the predefined blood levels was 10.9 ± 3.5 days (range, 5–21) for mirtazapine and 13.6 ± 4.6 days (range, 7–25) for imipramine. Including the 4-week treatment at this blood level, the mean ± SD total period on study medication (phase 1) was 38.9 ± 3.5 days (range, 33–49) for mirtazapine and 41.6 ± 4.6 days (range, 35–53) for imipramine.

Table 1. Total Study Population (N = 100)*

Variable	Mirtazapine (N = 50)	Imipramine (N = 50)
Age (y), mean ± SD (range)	45 ± 11 (23–64)	47 ± 10 (27–65)
Sex, male/female	12/38	11/39
Diagnosis		
Major depressive episode (DSM-III-R)	50	50
Unipolar	45	50
Nonpsychotic, 1st episode	16	22
Nonpsychotic, recurrent	15	14
Psychotic, 1st episode	8	10
Psychotic, recurrent	6	4
Bipolar	5	0
Nonpsychotic	4	0
Psychotic	1	0
Melancholic type	46	42
Major depressive episode (RDC)	50	49
Retarded depression (RDC)	15	15
Agitated depression (RDC)	16	17
Endogenous depression (RDC)	50	47
Suicidal	25	31
HAM-D baseline total score, mean ± SD (range)	26.3 ± 4.6 (19–37)	26.3 ± 5.08 (18–37)
MADRS baseline, total score, mean ± SD (range)	37.6 ± 6.0 (25–51)	36.0 ± 6.9 (16–54)
Duration current episode		
≤ 1 year	32	30
> 1 year	18	20
Adequate pretreatment with antidepressants	21	21
Family history (first/second degree)		
Depression	27	32
Suicide	10	9
Personality disorder	10	7

*Values are number of patients unless otherwise indicated.
Abbreviations: HAM-D = Hamilton Rating Scale for Depression, MADRS = Montgomery-Asberg Depression Rating Scale, RDC = Research Diagnostic Criteria.

According to the main response criterion at 4 weeks after attaining the predefined blood level, 33 (37%) of 90 were responders and 57 (63%) of 90 were nonresponders. Thus, 57 nonresponders (35 taking mirtazapine and 22 taking imipramine) were started on lithium addition. Lithium was added to the study medication after a mean lag time of 3.5 days. During phase 2, no patients dropped out because of adverse effects. Three patients dropped out for other reasons: 1 taking mirtazapine was treated with elec-

Table 2. Dropouts and Noncompleters by Noncompliance (N = 13) During Mirtazapine or Imipramine Monotherapy (Phase 1) and During Lithium Addition (Phase 2)

Treatment	Reason for Leaving Study	N
Mirtazapine		
Phase 1	Transfer to other ward	1
	Refuse to take medication	1
	Noncompliance[a]	1
Phase 2	Deterioration → ECT	1
	Noncompliance	1
Imipramine		
Phase 1	Mania	1
	Orthostasis	1
	Deterioration	1
	Fever and delirium	1
	Allergic reaction	2
	Noncompliance[a]	1
Phase 2	Discharge without our consent	1

[a]Noncompliance determined by low plasma drug levels.

Table 3. Number of Patients Receiving Comedication During Mirtazapine or Imipramine Monotherapy (Phase 1) and During Lithium Addition (Phase 2)

Comedication	Mirtazapine	Imipramine
Lorazepam		
Phase 1	4	2
Phase 2	8	3[a]
Total	8	4
Haloperidol		
Phase 1	7	4
Phase 2	0	1[b]
Total	7	4

[a]One patient stopped taking lorazepam before entering phase 2, and 1 patient continued this comedication.
[b]One patient who received haloperidol in phase 1 entered phase 2 with this comedication.

troconvulsive therapy after 10 days of lithium addition, because of worsening of the depression, and 1 patient taking imipramine was discharged without our consent after 11 days of lithium addition. A third patient had to be excluded from analyses because the monitored blood levels of mirtazapine showed noncompliance. Thus, 54 patients completed phase 2; 33 taking mirtazapine and 21 taking imipramine. The mean ± SD total period of lithium addition, including the time to reach the lithium blood level of 0.5–1.0 mmol/L, was 22.4 ± 5.0 days (range, 13–32) for patients receiving mirtazapine and 23.2 ± 5.0 days (range, 18–33) for those receiving imipramine.

Comedication (Table 3)

Twenty patients received comedication (8 received haloperidol, 3 haloperidol and lorazepam, and 9 lorazepam). Before lithium addition, lorazepam was administered to 6 patients (4 taking mirtazapine and 2 taking imipramine) (Table 3). During lithium addition, lorazepam was administered to another 6 patients (4 taking mirtazapine and 2 taking imipramine). Before lithium addition, 11 of the 29 psychotic patients (7 taking mirtazapine and 4 taking imipramine) were treated with between 4 and 12 mg/day of haloperidol during 9 to 40 days. Only 2 of those patients (1 taking mirtazapine and 1 taking imipramine) were responders; the other 9 were nonresponders. The MADRS score after haloperidol addition with these 9 patients was the same as or higher than before haloperidol addition. Thus, none of these patients benefitted from haloperidol, and all were subsequently treated with lithium addition. One of these patients, taking imipramine, entered the lithium addition period with this comedication, which was continued during the entire period of lithium addition.

Table 4. Results of Survival Analyses Comparing the 2 Treatment Strategies With Each Covariable Separately*

Covariable	Hazard Ratio	95% Confidence Interval	p Value
Baseline severity (HAM-D score)	1.01	0.95 to 1.06	.582
Duration of present episode (> 1 y)	0.32	0.17 to 0.60	.000
Number of previous depressions	1.04	0.90 to 1.19	.597
Bipolar type (yes)	1.40	0.42 to 4.72	.585
Adequate pretreatment (yes)	0.45	0.25 to 0.79	.005
Melancholic type (yes)	2.40	0.86 to 6.96	.093
Psychotic features (yes)	2.16	1.23 to 3.83	.008
Retarded depression (RDC) (yes)	0.89	0.49 to 1.69	.695
Agitated depression (RDC) (yes)	0.71	0.40 to 1.26	.241
Endogenous depression (RDC) (yes)	1.89	0.44 to 8.08	.390
Haloperidol (time-dependent) (yes)	1.24	0.52 to 2.92	.629
Time to attain predefined blood level of antidepressant (d)	0.99	0.93 to 1.06	.784

*The hazard ratio is the factor by which the response rate is multiplied for each unit increase in the covariable.

Treatment Effects

Survival analyses. The survival analysis of the total patient group (N = 100) with type of treatment as independent variable showed a significant difference between the 2 treatment groups (hazard ratio = 1.75; 95% CI = 1.03 to 3.00; p = .04). The results of the survival analyses with several covariables are presented in Table 4. The covariables "duration of present episode," "adequate pretreatment during current episode," and "psychotic features" showed a significant contribution to treatment results. No other covariable was significant, although "melancholic type" approached significance (see Table 4). There were no significant interactions of covariables with treatment, although the interaction of "psychotic features" with treatment type almost reached statistical significance (p = .06).

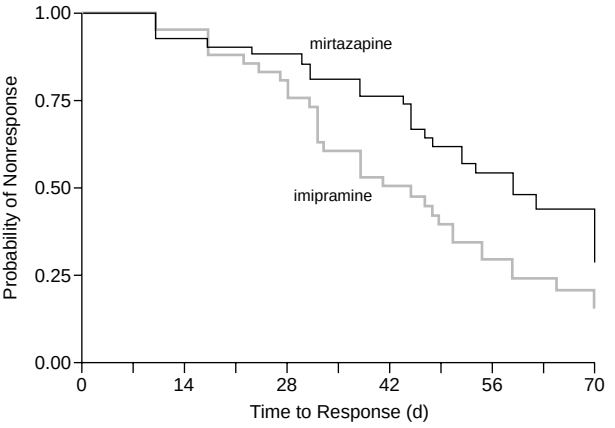
Next, we tested a model containing only the significant covariables in addition to type of treatment together (Table 5, Model 1). From this model we deleted 1 covariable with the highest p value ("adequate pretreatment"). This led us to the final model containing the covariables "duration of present episode" and "psychotic features" in addition to type of treatment; both covariables did improve the precision of the estimated difference between the 2 treatment groups (Table 5, Model 2).

The probability of nonresponse (Kaplan-Meier curve) of the 2 treatment groups in time is shown in Figure 2.

Table 5. Two Models of Survival Analyses Comparing the 2 Treatment Strategies, Using the Significant Covariables From Table 4

Variable	Hazard Ratio	95% Confidence Interval	p Value
Model 1			
Type of treatment (imipramine)	2.04	1.18 to 3.51	.010
Duration of present episode (> 1 y)	0.39	0.21 to 0.76	.005
Adequate pretreatment (yes)	0.58	0.32 to 1.05	.074
Psychotic features (yes)	1.71	0.96 to 3.03	.068
Model 2			
Type of treatment (imipramine)	2.08	1.21 to 3.58	.009
Duration of present episode (> 1 y)	0.35	0.19 to 0.66	.001
Psychotic features (yes)	1.82	1.03 to 3.22	.040

Figure 2. Probability of Nonresponse (Kaplan-Meier Curve) for the 2 Treatment Groups Over Time: Mirtazapine Plus Lithium Addition (N = 50) and Imipramine Plus Lithium Addition (N = 50), (p = .04)



Numbers of responders. In order to obtain some insight into the contribution of each of the significant covariables separately, the proportion and percentage of responders at the end of each treatment phase are presented in Table 6. These numbers illustrate the result of the survival analysis. Both long duration of the present episode and adequate pretreatment are related to poor response, although as much in the imipramine group as in the mirtazapine group. It must be pointed out that these covariables are highly related, as 26 (68%) of 38 patients with a duration of the present episode > 1 year had an adequate pretreatment of the present episode, compared with 16 (26%) of 62 with a duration of ≤ 1 year. Table 6 also illustrates that the superiority of imipramine is more pronounced in the group of psychotic patients.

DISCUSSION

The purpose of the present study was to compare the overall effectiveness of a 2-step treatment strategy with a standard tricyclic antidepressant and subsequent lithium addition with a similar treatment strategy with a modern antidepressant and subsequent lithium addition. For the clinician, it is important to know which of these 2 strategies results in an optimal chance for the patient to recover in the shortest period of time. The results of the survival analysis, in which all patients started on treatment are included (intent-to-treat), indicate a significant difference in favor of imipramine and subsequent lithium addition. According to the analyses that used several baseline variables as covariables, "duration of present episode," "adequate pretreatment," and "psychotic features" are significant predictors for response (see Table 4). In 2 different models, these covariables improved the precision of the estimation of the difference between the 2 treatment strategies (see Table 5).

The fact that no significant interaction between any of the 3 significant covariables and treatment type was observed indicates that these baseline variables did not contribute significantly to the difference between the 2 treatments. Thus, both treatment strategies show less effect in patients with a duration of present episode > 1 year and in patients with adequate pretreatment of present episode (baseline variables that often go hand in hand), as also reported in the analysis of phase 1 of this study.[11] However, there was an almost significant interaction between the baseline variable "psychotic features" and treatment type. Thus, it is possible that psychotic patients profited more than nonpsychotic patients from the superiority of imipramine. These results emphasize the value of lithium addition to tricyclics, especially for patients with psychotic depressions, as has been suggested in earlier reports.[17–19]

No other covariables were significant in these analyses. This was especially of importance for the unequally divided baseline variable "bipolar"; the 5 bipolar patients were by chance all included in the mirtazapine group (Tables 1 and 4), but according to the analysis, this fact did not influence the response rate in the mirtazapine group.

It may be argued that the overall response was influenced by haloperidol, received by 7 patients taking mirtazapine and 4 patients taking imipramine. However, of these 11 patients, only 2 (1 taking mirtazapine and 1 taking imipramine) were responders before lithium addition, indicating that haloperidol was not instrumental in the recovery of those patients. Moreover, a survival analysis with haloperidol intake as time-dependent covariable showed no significant contribution to the results (Table 4).

Thus, in a group of severely depressed inpatients, the treatment strategy of imipramine administration with subsequent lithium addition for nonresponders is more effective than the same strategy with mirtazapine and lithium addition (76% vs. 53% responders, respectively), as is also evident from the intent-to-treat analysis (64% vs. 48% responders). The advantage of imipramine is in part

Table 6. Number and Percentage of Responders at the End of Phase 1 and Phase 2 by Covariables That Contributed Significantly to the Results in the Survival Analysis

	Intent-to-Treat								Completers							
	Mirtazapine				Imipramine				Mirtazapine				Imipramine			
	Phase 1		Phase 2		Phase 1		Phase 2		Phase 1		Phase 2		Phase 1		Phase 2	
Variable	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%
Total group	12/50	24	24/50	48	21/50	42	32/50	64	12/45	27	24/45	53	21/42	50	32/42	76
Psychotic																
Yes	4/15	27	7/15	47	9/14	64	12/14	86	4/12	33	7/12	58	9/12	75	12/12	100
No	8/35	23	17/35	49	12/36	33	20/36	56	8/33	24	17/33	52	12/30	40	20/30	67
Duration																
≤ 1 year	9/32	28	19/32	59	18/30	60	24/30	80	9/27	33	19/27	70	18/27	67	24/27	89
> 1 year	3/18	17	5/18	28	3/20	15	8/20	40	3/18	17	5/18	28	3/15	20	8/15	53
Pretreatment																
Not adequate	10/29	34	15/29	52	16/29	55	23/29	79	10/25	40	15/25	60	16/27	59	23/27	85
Adequate	2/21	10	9/21	43	5/21	24	9/21	43	2/20	10	9/20	45	5/15	33	9/15	60

offset by the higher number of treatment failures due to side effect–related dropout; during phase 1, 6 of 7 dropouts that occurred with imipramine treatment were caused by adverse effects as compared with none of 3 that occurred with mirtazapine treatment.

Most open and double-blind studies with respect to lithium addition have involved nonresponders to antidepressants for which response and dropout percentages of phase 1 are not reported[1]; in fact, the antidepressants involved often were not listed. Thus, the overall effectiveness of treatment with the antidepressant and of subsequent lithium addition can not be estimated. The present results illustrate the importance of this issue: the comparison between the results of lithium addition to imipramine nonresponders and to mirtazapine nonresponders, respectively (i.e., analysis of the results of phase 2 without taking into account phase 1), could suggest equal efficacy of lithium addition to both antidepressants. However, this is not an appropriate comparison, since in our study mirtazapine is less effective than imipramine, and the patient populations entering the lithium addition phase are not therefore comparable.

Regarding the difference in effectiveness between mirtazapine and imipramine in phase 1, one could argue that adjusting the dose of both drugs to attain fixed blood levels could have influenced the results because this procedure is not a validated one for mirtazapine as it is for imipramine. However, the mean mirtazapine dose of 76 mg/day (range, 40–100 mg) was above the dose used in other inpatient studies,[11] which does not make probable a reduced response rate due to the fixed blood level.

It must be emphasized that our results can not be generalized to patient populations other than this group of severely ill inpatients, of whom many (29%) were psychotic. Trials similar to the present one in other patient populations are needed for further generalization.

Taking into account the literature on the efficacy of tricyclic antidepressants in severely depressed inpatients,[11,20,21] we translate our results into clinical practice as follows. We start with imipramine treatment at fixed blood levels and, if necessary, add lithium, which is sufficient and effective for the majority of patients. The risk of more common as well as more severe adverse effects is accepted, because this risk does not offset the superior overall effectiveness of imipramine. In the case of troublesome or severe side effects, the patient is shifted to a modern antidepressant such as mirtazapine without losing much time in treatment, and, if necessary, lithium is added to this antidepressant.

Drug names: haloperidol (Haldol and others), imipramine (Tofranil and others), lorazepam (Ativan and others), mirtazapine (Remeron).

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